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Author
Marder, Stephen R

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The NIMH-MATRICS project for developing cognition-enhancing agents for schizophrenia

Stephen R. Marder, MD

The US National Institute of Mental Health supported an initiative to facilitate the development of pharmacological agents for enhancing neurocognition in patients with schizophrenia. This has been accomplished through a consensus-building process that has included representatives from academia, the pharmaceutical industry, and government. The group has addressed obstacles to drug development that include (i) the lack of a well-accepted instrument for measuring neurocognition in clinical trials; (ii) the lack of a consensus on the best molecular target or targets for drug development; (iii) the lack of a consensus regarding the optimal trial design for either comedication that improves cognition when added to an antipsychotic or a broad spectrum agent that improves cognition and treats psychosis; and (iv) the approaches of regulatory agencies such as the US Food and Drug Administration to approving and labeling a new agent.

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Author affiliations: Semel Institute of Neuroscience, University of California at Los Angeles, Calif, USA

Address for correspondence: Building 210, Room 130, West Los Angeles Veterans' Affairs Health Care Centre, Los Angeles, CA 90073 USA
(e-mail: marder@ucla.edu)

The US National Institute of Mental Health (NIMH) developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative for a number of reasons: (i) there is a widespread belief that too few innovative new drugs are being developed for illnesses that affect the central nervous system (CNS) in comparison to other areas of medicine[1]; (ii) drugs for CNS disorders have often been accidental discoveries rather than the products of well-developed scientific strategies[2]; and (iii) there is dissatisfaction with the effectiveness of drugs for schizophrenia. Evidence for this comes from the recent publication of a large trial comparing the effectiveness and side effects of several second-generation antipsychotics known as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial.[3] In this study, 74% of patients were discontinued from their antipsychotic treatment due to lack of efficacy or side effects.

The results of the CATIE trial emphasize that there are important limitations in what antipsychotics can do for patients. Patients and clinicians tend to be dissatisfied with the clinical response or the tolerability of available agents. In addition, the widespread availability of these drugs has not resulted in long-term improvements in the outcome of schizophrenia.[4] These observations, along with the recent interest in recovery and improving functional outcomes, suggest that drug development for schizophrenia should focus on targets other than dopamine D_2 receptors.

Impaired neurocognition in schizophrenia

The focus on neurocognition is based on a number of factors. First, impairments in neurocognition are core features of schizophrenia. These impairments are present during acute exacerbations of the illnesses and dur-

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ing periods of remission. In addition, first- and second-generation antipsychotics are relatively ineffective at treating these symptoms. Patients treated with these agents tend to have continuing deficits even when adequately treated with antipsychotics.[5] Further, the neurocognitive deficits tend to be relatively severe. A meta-analysis by Heinrichs and Zakzanis[6] demonstrates that the impairments in schizophrenia are particularly severe for memory, attention, and executive function. In these areas, individuals with schizophrenia—on average—performed 1.5 standard deviations below community norms.

The most important reason for the focus on neurocognition may be that these impairments appear to be related to the functional outcomes of patients. A review by Green[7] found that the impairments in social and vocational functioning in schizophrenia were strongly related to the impairments in neurocognition. The magnitudes for the relationships between cognitive deficits and functional outcome are medium for individual cognitive constructs such as attention or working memory, but the relationships can be strong when summary scores (eg, composites of several cognitive functions) are used.[8-10] This literature on cognitive linkages to functional outcome provides a compelling rationale for intervention development at the level of cognition.

In contrast to cognitive deficits, clinical symptoms are only weakly related to functional outcome in schizophrenia.

Facilitating drug development

Hyman and Fenton[2] have suggested a strategy for drug development that focuses on dissecting psychiatric disorders into component dimensions of psychopathology that may be more closely related to pathophysiological processes. These components rather than the illnesses themselves may be more amenable to novel pharmacological approaches to therapeutics. This strategy encourages the development of new therapeutics for schizophrenia that move beyond positive symptoms as clinical targets to focus on dimensions of the illness most associated with functional disability.

The goal of the MATRICS initiative is to address important obstacles that are likely to interfere with the development of new pharmacological approaches to improving neurocognition in schizophrenia. These obstacles include (i) the lack of a well-accepted instrument for measuring neurocognition in clinical trials; (ii) the lack of a consensus on the best molecular target or targets for drug development; (iii) the lack of a consensus regarding the optimal trial design for either comedication that improves cognition when added to an antipsychotic or a broad-spectrum agent that improves cognition and treats psychosis; and (iv) the approaches of regulatory agencies such as the US Food and Drug Administration (FDA) to approving and labeling a new agent. The MATRICS group has attempted to address each of these obstacles.

Development of the MATRICS battery

The selection of the MATRICS battery emerged from a 2-year process that involved a broad range of individuals from academia, industry, and government. The process began with a process for determining the domains of neurocognition that would be evaluated as well as the criteria for selecting tests for each domain. The domains emerged from both factor analysis of existing databases and expert opinion.[11] Expert opinion was used to prioritize the criteria for test selection. *Table I* lists the criteria for test selection.

Approximately 90 tests were proposed for measuring performance in the eight domains. The characteristics of each test were evaluated and candidates were narrowed to 36. These tests were graded according to the criteria in *Table I* and further narrowed to one or two tests in each domain. These tests were then evaluated in a five-site MATRICS Psychometrics and Standardization Study. The tests were compared with one another in a diverse group of patients with schizophrenia. The results led to the final selection of the battery, which is listed in *Table II*.

- Valid assessment of cognition at the level of all individual major cognitive domains
- Inclusion of the following cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition
- High test-retest reliability
- High utility as a repeated measure
- Demonstrated relationship to functional outcome
- Demonstrated tolerability and practicality

Table I. Essential criteria for a consensus cognitive battery for clinical trials in schizophrenia.

Co-primary measures

At one of the MATRICS meetings, Thomas Laughren from the FDA confirmed that cognition in schizophrenia was a reasonable clinical target, but that his agency was unlikely to approve a drug based only on improvement on a neuropsychological test. Approval would require an outcome with greater face validity, though it would not be necessary to demonstrate that a drug actually improved patient functioning. He did agree that reasonable coprimary measures would be functional capacity measures or proxy measures that demonstrate an individual's ability to perform a task, and not whether they actually do it or a patient or caregiver's interview-based assessment of cognition.

With this in mind, we evaluated a number of potential measures of functional capacity and interview-based measures of cognition in the psychometric study. One instrument was selected to represent each domain: the Social Functioning Scale (SFS),[12] the SCORS (R. Keefe, personal communication), the Maryland Assessment of Social Competence (MASC),[13] and the UCSD Performance-Based Skills Assessment (UPSA).[14] The Clinical Global Impression (CGI)–Cogs (Bilder et al, personal communication) was added at a later time as an alternative interview-based measure. These measures were administered along with the MATRICS battery in the psychometric study and evaluated using similar criteria for the selection neuropsychological tests. The results indicated that all of the measures had reasonable psychometric properties. In addition, the measures had modest relationships with functioning and strong relationships with cognition.

Speed of processing	**Administration time (min)**
Category Fluency	2.0
Brief Assessment of Cognition in Schizophrenia (BACS) – Symbol-Coding	3.0
Trail Making A	2.1
Attention/vigilance	
Continuous Performance Test – Identical Pairs (CPT-IP)	13.4
Working memory	
Verbal: University of Maryland – Letter-Number Span	5.9
Nonverbal: Wechsler Memory Scale (WMS) – III Spatial Span	5.1
Verbal learning	
Hopkins Verbal Learning Test (HVLT) – Revised	4.1
Visual learning	
Brief Visuospatial Memory Test (BVMT) – Revised	4.7
Reasoning and problem solving	
Neuropsychological Assessment Battery (NAB) – Mazes	11.2
Social cognition	
Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) – Managing Emotions	12.0
Total estimated administration time of Provisional Cognitive Consensus Battery	**63.5**

Table II. The Provisional Cognitive Consensus Battery. The final composition of the battery will depend on reaching appropriate agreements for licensing and distribution of tests with the respective test developers and publishers. Once these agreements have been reached, the final consensus battery will be posted on the MATRICS Web site.

Trial design

An FDA-MATRICS consensus meeting on trial design brought together a group of neuropsychologists, clinical trialists, industry representatives, and representatives from the NIMH and the FDA. The meeting included a wide-ranging discussion of issues including subject selection, statistical issues, and design issues. The meeting focused on issues that should be addressed for either a comedication that would be added to an antipsychotic or a broad-spectrum antipsychotic that would be effective for psychotic symptoms and at enhancing cognition. The consensus recommendations are published in a special article by Robert Buchanan in *Schizophrenia Bulletin.*[15] Here are some of the recommendations:

- Include subjects who are clinically stable.
- Exclude subjects only if impairment compromises test validity or if they perform at ceiling.
- For comedication, compare addition of drug or placebo to current antipsychotic.
- For a broad-spectrum antipsychotic, compare experimental drug to an antipsychotic that does not impair cognition.
- Monitor outcome with MATRICS battery and a coprimary measure of functional capacity or interview-based cognitive assessment.

Molecular targets

We also developed a process to develop a consensus regarding the molecular targets that should be a focus of drug development. This was carried out under the lead-

ership of Carol Tamminga and Mark Geyer. We first interviewed a large group of neuroscientists and asked them to rank the targets. We then assembled a group of experts at an open meeting at the National Institutes of Health in Bethesda, Maryland. Proponents of each target presented the evidence for each target and there was a broad open discussion of each. After the meeting the group was surveyed leading to this list of targets. *Table III* provides the ranking of the first 9 targets. α_7-Nicotinic agonists and dopamine D_1 agonists were viewed as particularly promising. There was also considerable interest in subtypes of glutamate receptors.

Other activities in this area are currently taking place as MATRICS activities are completed. First, the MATRICS battery is being assembled so that it can be purchased as a single package. Second, NIMH has funded a trials network that is initiating studies of promising drugs. ❑

Target	Ranking
α_7-Nicotinic receptor agonists	1
Dopamine D_1 receptor agonists	2
AMPA glutamatergic receptor agonists	3
α_2-adrenergic receptor agonists	4
NMDA glutamatergic receptor agonists	5
Metabotropic glutamate receptor agonists	6
Glycine reuptake inhibitors	7
M_1 muscarinic receptor agonists	8
$GABA_A$ R subtype selective agonists	9

Table III. Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) ranking of targets. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

El proyecto MATRICS del NIMH para desarrollar agentes que mejoren la cognición en la esquizofrenia

El Instituto Nacional de Salud Mental de los Estados Unidos ha financiado una iniciativa para facilitar el desarrollo de psicofármacos para mejorar la neurocognición en pacientes con esquizofrenia. Esto se ha llevado a cabo mediante un proceso consensuado en que se han incluido representantes del mundo académico, de la industria farmacéutica y del gobierno. El grupo ha señalado los obstáculos para el desarrollo de fármacos, los que incluyen: (i) la falta de un instrumento bien aceptado para medir la neurocognición en los ensayos clínicos, (ii) la falta de consenso respecto al mejor o los mejores objetivos moleculares para el desarrollo de fármacos, (iii) la falta de consenso respecto al diseño de ensayos óptimos tanto para la comedicación que mejore la cognición cuando se asocia a un antipsicótico como para un fármaco de amplio espectro que mejore la cognición y trate la psicosis y (iv) los procedimientos de las agencias reguladoras, como la FDA de los Estados Unidos, para aprobar y clasificar un nuevo fármaco.

Le projet NIMH-MATRICS pour développer des agents stimulant la cognition dans la schizophrénie

L'institut national américain de santé mentale a soutenu une initiative pour permettre le développement de médicaments stimulant la neurocognition des patients atteints de schizophrénie. Un regroupement consensuel comprenant des représentants de l'académie, de l'industrie pharmaceutique et du gouvernement a permis d'y arriver. Le groupe a présenté les obstacles au développement des médicaments : 1°: le manque d'instruments faisant l'unanimité pour mesurer la neurocognition dans les études cliniques ; 2°: le manque de consensus sur la meilleure cible moléculaire ou sur les cibles pour développer les médicaments ; 3°: le manque de consensus vis-à-vis du schéma optimal à adopter pour l'étude soit d'une comédication améliorant la cognition lorsqu'elle est ajoutée à un antipsychotique soit d'une molécule à large spectre améliorant la cognition et traitant la psychose ; et 4°: l'approche des administrations telles que la FDA (Food and Drug Administration) pour homologuer et cataloguer un nouveau médicament.

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